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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/571,989	03/13/2006	Michael Kalafatis	CSU-17999	5552

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EXAMINER	
BARNHART, LORA ELIZABETH	

ART UNIT	PAPER NUMBER
1651	

MAIL DATE	DELIVERY MODE
12/17/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/571,989	KALAFATIS, MICHAEL	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8,10,43-49,51 and 112-142* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8,10,43-49,51 and 112-142* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments

Applicant's amendments filed 8/27/09 to claims 43, 120, 128, and 136 have been entered. No claims have been cancelled or added in this reply. Claims 1-5, 8, 10, 43-49, 51, and 112-142 remain pending in the current application, all of which are being considered on their merits. References not included with this Office action can be found in a prior action. Any rejections of record not particularly addressed below are withdrawn in light of the claim amendments and applicant's comments.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 8, 10, 43-49, 51, and 112-142 are/remain rejected under 35 U.S.C. 103(a) as being unpatentable over Hortin (1990, *Blood* 76: 946-952; reference AM on 3/13/06 IDS) taken in view of Pittman et al. (1994, *Biochemistry* 33: 6952-6959; reference AO on 3/13/06 IDS), Bakker et al. (1994, *Journal of Biological Chemistry* 269: 20662-20667), and Ramabhadran (1994, *Pharmaceutical Design and* Development, Ellis Horwood, New York NY, pages 40, 42, and 43).

Hortin teaches that the complete sequence of human coagulation factor V (hereafter "Factor V") was known at the time of the invention and that said sequence includes the sequence DYDYQ (and, therefore, DYDY; page 946, column 1, paragraph 2; and Figure 6 at page 950, e.g.). Hortin teaches that Factor V is sulfated *in vivo* and suggests that the tyrosine residues at positions 696 and 698 are among the residues that are sulfated (page 950, column 2). Hortin speculates that thrombin binding to Factor V may be mediated by binding to these sites (page 951, column 1); this conclusion is based in part on the fact that sulfation of tyrosine residues in other proteins modulates their direct binding to thrombin (page 946, column 2). Hortin teaches a solution comprising Factor V (page 946, column 2, last paragraph).

Hortin does not teach any fragments of Factor V, e.g. the tetrapeptide DYDY or the pentapeptide DYDYQ. Hortin does not exemplify a peptide in which one or both of the tyrosines in the DYDY or DYDYQ motif are sulfated.

Pittman teaches that inhibiting sulfation of Factor V inhibits its procoagulant activity (page 6955, column 1, under "Sulfation is required..."). Specifically, Pittman teaches that Factor V must be sulfated to undergo binding and subsequent cleavage by

thrombin (page 6956, column 1; and Figure 3B). Pittman concurs with Hortin that tyrosines 696 and 698 are likely candidates for the sulfation (page 6957, column 1, under "Discussion"). Pittman also teaches methods for sulfating proteins (pages 6953 and 6954).

Bakker teaches that the portion of Factor V heavy chain required to bind thrombin is the C-terminal 27 amino acids thereof, which comprises the DYDYQ motif (see Table II at page 20665 and page 20664, column 1, first full paragraph). Bakker further teaches that these 27 amino acids are responsible for the binding of Factor V to prothrombin (page 20667, column 1, first full paragraph).

Ramabhadran teaches that small peptides (i.e., up to 50 amino acids) may be made in high yield and with high purity by synthesizing them chemically from their constituent amino acids (page 43). Ramabhadran teaches that chemically synthesized peptides are useful in the laboratory as drugs (page 43, third full paragraph).

The person of ordinary skill in the art would have had a further reasonable expectation of success in producing short peptides including tyrosine residues 696 and 698 because Hortin teaches that the entire sequence of Factor V was known at the time of the invention and because Ramabhadran teaches that peptides of up to 50 amino acids in length and with a given sequence may be chemically synthesized. The skilled artisan would have been motivated to produce such peptides because Bakker teaches that the C-terminal portion of Factor V heavy chain, which comprises tyrosine residues 696 and 698, is the domain required to bind prothrombin; the skilled artisan would have been motivated to determine which of these 27 residues is necessary for the interaction

and which are not. Furthermore, sulfating these residues would have constituted routine experimentation on the part of the skilled artisan, since Pittman teaches methods for doing so. The skilled artisan would have been motivated to sulfate the tyrosine residues because Pittman and Horton both teach that they may be sulfated *in vivo*, because Bakker teaches that these residues are within a domain that binds prothrombin, and because Pittman teaches that Factor V must be sulfated to bind thrombin. Therefore, the skilled artisan would have endeavored to learn whether the tyrosine residues in the 27-amino acid peptide of Bakker need be sulfated to bind prothrombin. In light of the practical teachings and predictions of the art, the determination of the peptide sequence and sulfation pattern would have constituted routine experimentation at the time of the invention. See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

The skilled artisan would have had a reasonable expectation that peptides made as suggested by the art as set forth above would inhibit thrombin activity because Hortin teaches that Factor V is bound and cleaved by thrombin, Bakker teaches that the C-terminal 27 amino acids of Factor V are the portion involved in binding thrombin, and Pittman and Horton teach that residues 696 and 698 are likely required for thrombin binding. See *KSR*.

A person of ordinary skill in the art would have had a reasonable expectation of success in sulfating either or both of the tyrosine residues at positions 696 and 698 within Factor V because Hortin and Pittman both teach that these residues are within consensus sequences for sulfation. The skilled artisan would have been motivated to

sulfate one or both of these residues in Factor V because Pittman teaches that Factor V is not active unless it is sulfated.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to produce peptides using the method of Ramabhadran that correspond to various portions of the 27 amino acids of Factor V taught by Bakker to be involved in binding thrombin in order to determine which portions of this fragment are necessary for thrombin binding. It would have been further obvious to sulfate one or more of the tyrosine residues within the resulting peptide because Pittman teaches that sulfation is required for activity and teaches methods for sulfating proteins.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Applicant alleges that the claims are not drawn merely to a peptide. See pages 17 and 20. Applicant alleges that the cited art provides no express motivation to make the peptides DYDY or DYDYQ. See pages 11-12, 14-15, 17, and 20-22. Applicant alleges that the age of the references is relevant. See page 12. Applicant alleges that the field of art is unpredictable. See pages 18-19. Applicant alleges that if the claimed invention were obvious, skilled artisans would have disclosed it prior to the invention. See pages 22-23. These arguments have been fully considered, but they are not persuasive.

From the examiner's perspective, the primary misunderstanding in this case is the statutory class of invention to which these claims are drawn. The instant claims are absolutely drawn to peptides, not to any process in which they may participate. The

application originally contained claims to methods of treatment and methods of inhibiting thrombin generation, but these claims were canceled prior to the first Office action on the merits; had they been included at the time of initial examination, a restriction requirement would have been in order. Peptides have myriad uses beyond those envisioned by applicant. Establishing that it would have been obvious to make a particular peptide does not require establishing that skilled artisans would have been motivated to make that peptide for the same reasons as applicant. Applicant's statement at page 17 that the claims "also expressly recite thrombin" is a mischaracterization of the claims. Statements of intended use, such as "for direct binding to thrombin," do not affect the patentability of the claimed product. Compositions are defined by their physical, structural, and chemical properties, not by an intended use or application. See M.P.E.P. § 2111.02. As always, the claims have been interpreted as being drawn to compositions and not to any processes.

As to applicant's comments alleging that the art does not provide motivation to make the claimed peptides, recent caselaw has established that there is no requirement that the cited art expressly recite a motivation to combine its teachings. In *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), the Supreme Court determined that motivation to combine prior art references need not be explicitly stated in the cited prior art; "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation

but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103." *Id.* at 1397. Recently, the CAFC affirmed *KSR* as it pertains to biological problems in *In re Kubin*, 90 USPQ2d 1417 (Fed. Cir. 2009). In *Kubin*, the CAFC determined that a nucleic acid molecule encoding a particular peptide would have been obvious, given the fact that the peptide had a known function and the methods for determining relevant peptide sequences and making corresponding nucleotides were conventional in the art. *Id.* at 1419-20.

The situation in this case is similar to that in *KSR*, because Bakker, Pittman, and Hortin had identified the last 27 amino acids of Factor Va as being important in the protein's function, and Ramabhadran teaches methods for producing peptides. Even if the art had not recognized the importance of the last 27 amino acids in Factor Va's function (which the examiner does not concede), Factor Va is a protein of limited length and known sequence, so by definition, there are only a finite number of identified, predictable solutions to the question of which amino acids account for a given activity.

The fact pattern in this case also parallels that in *Kubin*, since the function and sequence of Factor Va was known at the time of filing, as were methods for designing and synthesizing peptides of a given sequence. Taken together in light of the relevant recent caselaw, the cited references fairly identify the C-terminal 27 amino acids of Factor Va, and in particular a few residues around the portion of Factor Va cleaved by thrombin, as a region of interest in the protein's interaction with thrombin and provide a motivation and a protocol for investigating that region further. Even in light of the opinion declarations submitted by the inventor, it is not clear what properties of these

peptides are truly unexpected and surprising, given the fact that Hortin teaches that sulfated residues were known at the time to be important in peptides that interact with thrombin, and Hortin teaches sulfated residues in the C-terminal portion of Factor V near the residue at which thrombin cleaves Factor Va. "The fact that appellant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious." *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Comments regarding the age of the references are, and will remain, unpersuasive. "The mere age of the references is not persuasive of the unobviousness of the combination of their teachings, absent evidence that, notwithstanding knowledge of the references, the art tried and failed to solve the problem." *In re Wright*, 569 F.2d 1124, 1127, 193 USPQ 332, 335 (CCPA 1977). See M.P.E.P. § 2145. There is no evidence in this case that other investigators tried and failed to identify relevant peptides within Factor Va; indeed, all of the cited art points toward the same conclusion, namely that the C-terminal portion of Factor Va is biologically relevant and that skilled artisans have been narrowing down the key residues within that region for years.

Applicant's allegation that the field is unpredictable is also not supported by any evidence. The prior art references clearly teach that Factor Va participates in thrombin processing, that Factor Va is cleaved by thrombin near residues 696 and 698, and that the C-terminal portion of the protein contains important residues that, in light of prior art teachings referenced by Hortin, be sulfated to modulate Factor Va's activity. Applicant has repeatedly mischaracterized the teachings of Bakker, leading to a key

misunderstanding in this prosecution. Bakker teaches that a cleavage product of Factor Va (Va_{NO}), which lacks Factor Va's C-terminal 27 amino acids, is "impaired in its ability to interact with Factor Xa and prothrombin." See the abstract of Bakker. The clear implication of this statement is that the C-terminal amino acids are necessary for Factor Va's activity. Applicant's own work published after the instant filing characterizes Bakker as supporting the conclusion that "the carboxyl-terminal portion of the heavy chain of Factor Va (residues 680-709) is responsible for the interaction of Factor Va with one or both components of prothrombinase." See Beck et al., *Journal of Biological Chemistry* 279: 3084-3095 at 3085, column 1; reference AN on 3/13/06 IDS. Furthermore, Hortin teaches that Factor V is cleaved by thrombin around residues 696 and 698, i.e. that it is bound by thrombin at that region. See Figure 6, e.g.; the basis for applicant's repeated contention that Factor Va binds prothrombin but not thrombin is unclear, given Horton's teachings. In any case, the examiner again emphasizes that the claims are not drawn to any method of inhibiting thrombin and that statements of intended use do not, on their own, distinguish a claimed peptide from a peptide with exactly the same sequence that is fairly suggested and enabled by the prior art. Despite applicant's arguments and implications to the contrary, the claims in this prosecution are drawn to peptides and compositions of peptides, nothing more.

There is no evidence of unexpected results on record. In *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), the Supreme Court reiterated the standard for overcoming obviousness rejections initially set forth in *Graham v. Deere*, namely convincing arguments that the cited art is non-analogous, a showing that the

prior art teaches away from the claimed invention, or a showing of secondary considerations, *e.g.* truly unexpected results (see *KSR* at 1399). The declaration of inventor Kalafatis under 37 C.F.R. 1.132 included with the instant reply and alleging the presence of unexpected results (hereafter "the Kalafatis declaration") has been fully considered, but it appears to amount to the inventor's own opinion that the results in the specification were "surprising and unexpected" and/or "remarkable." See sections 9-14 of the Kalafatis declaration. In assessing the probative value of an expert opinion such as the Kalafatis declaration, the examiner must consider the nature of the matter sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985), *cert. denied*, 475 U.S. 1017 (1986), And M.P.E.P. § 716.01(c). In this case, the matter applicant seeks to establish allegedly surprising results present in the specification, but as discussed above, there is no comparative basis for identifying any unexpected properties. The fact that a peptide known to bind the protein of interest has more of an effect on inhibition than no inhibitor at all, as shown in Figures 10 and 11, e.g., cannot be considered "surprising." The Kalafatis declaration refers to "relatively low concentrations" of the DYDY and DYDYQ peptide, but again, no experimental basis for comparison is provided to support this statement. There is no comparison of the DYDY and DYDYQ to other less effective peptides, data that might support applicant's claim of unexpected results and/or a critical sequence from the art-recognized 27-amino acid C-terminus of Factor Va. The expert making the declaration

is the inventor and therefore clearly has an interest in the outcome of the case. In light of the strong case for obviousness made by the examiner, the Kalafatis declaration is unpersuasive of error.

With all due respect, applicant's question as to some connection between a failure of the prior art to disclose the invention as claimed and the obviousness of the invention has been fully addressed within the section 103 rejection. The examiner maintains that the prior art does fairly disclose applicant's invention because the references teach the sequence and function of Factor Va, investigations as to its functional domains, and methods for synthesizing peptides. Applicant is reminded that a failure of the prior art to exemplify the claimed composition does not constitute a failure to disclose it.

No claims are allowed. No claims are free of the art.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is (571)272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651